ORIGINAL RESEARCH

Prevalence of von Willebrand Disease in Patients with Heavy Menstrual Bleeding: An Indian Perspective

Shuchi Jain[1], Nisha R Agrawal[2], Vijai Tilak[3], Madhu Jain[4], Tej B Singh[5], Krishna S Piplani[6]

Abstract

Aim: The von Willebrand disease (vWD) is said to be the most common hemostatic disorder among the nonstructural causes of heavy menstrual bleeding (HMB). This study was carried out to find prevalence of vWD and its subtypes in patients with HMB referred to a tertiary healthcare center.

Materials and methods: Two hundred patients with HMB and equal number of age-matched control were subjected to laboratory tests such as complete blood count, bleeding time, and clotting time. Prothrombin time (PT), activated partial thromboplastin time (APTT), and factor VIII (FVIII):C assay were done manually. von Willebrand factor (vWF:Ag) antigen assay and vWF:Ag collagen binding (CB) were done by enzyme-linked immunosorbent assay (ELISA). Platelet aggregation study with ristocetin was done to find the different subtypes of vWD.

Results: vWD and its subtypes were diagnosed in 25 out of 200 women with HMB with a prevalence of 12.5%. Type III vWD was the commonest (15/25, 60%), followed by type II (7/25, 28%) and type I (3/25, 12%). Among the various subcategories of type II, type IIB was conspicuously absent and type IIN was the most frequent (5/7, 71%).

Conclusion: vWD should always be considered as one of the possible bleeding disorders in patients with HMB particularly in those referred to a tertiary care center. It was detected in 12.5% of such women, and type III was the most frequent type encountered among its various subtypes.

Clinical significance: Detection of vWD and its various subtypes at the earliest opportunity would help the treating physician to plan out a definite line of management and save many women from unwarranted hysterectomies and also improve their quality of life and reproductive potential.

Keywords: Case–control study, Congenital bleeding disorder, Heavy menstrual bleeding, Inherited bleeding disorder, von Willebrand disease, von Willebrand factor.

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Introduction

The heavy menstrual bleeding (HMB) is a condition when the average blood loss during the menstruation exceeds 80 mL per cycle, if the cycle lasts for more than 7 days or is associated with soaking a pad/tampon at least every 2 hours.[1,2] Among the nonstructural causes of HMB, the von Willebrand disease (vWD) is said to be the most common hemostatic disorder in approximately 13% of women with HMB.[3] This study was carried out to find the prevalence of vWD in the patients with HMB referred to our tertiary healthcare center as the entity is still underdiagnosed in our country and these patients are often subjected to unwarranted hysterectomies.

Materials and Methods

The study comprised of 200 women attending gynecology OPD with diagnosis of HMB and fulfilling the inclusion criteria. The controls included an equal number of age-matched women without menstrual irregularities. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institute ethical committee) and with the Declaration of Helsinki 1975, as revised in the year 2000.

Inclusion Criteria

The patients with HMB in three age-groups: <20, 20–44, and >44 years with normal pelvic examination (done only in married women), normal pelvic ultrasound, and with no previously diagnosed cause of HMB or associated systemic or endocrine disease were included.

[1,2,4]Department of Obstetrics and Gynecology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

[3]Department of Pathology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

[5]Division of Biostatistics, Department of Community Medicine, Institute of Medical Sciences, Varanasi, Uttar Pradesh, India

[6]Department of Biostatistics, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Corresponding Author: Madhu Jain, Department of Obstetrics and Gynecology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India, Phone: +91 9415302988, e-mail: drmadhujainbhu@gmail.com

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Exclusion Criteria

The patients with endocrine disorder, e.g., thyroid disease, pelvic pathology (fibroid, uterine polyp, gynecological malignancy, etc.), using intrauterine device or taking medications such as anticoagulants within the past 2 months, oral contraceptive pills within one cycle of participation, nonsteroidal anti-inflammatory drugs (NSAIDs) and platelet impairing medication or herbal medications within 14 days of participation, or having systemic

illness (liver disease, heart disease with anticoagulants/low-dose aspirin) were excluded from the study.

Following the informed consent, the patients and controls were subjected to laboratory tests. Nine milliliters of blood was collected in a centrifuge tube with 1 mL of 3.2% sodium citrate as anticoagulant (9:1 ratio). The sample was processed within 2 hours of blood collection or stored at an appropriate temperature of −70°C in laboratory. Platelet-rich plasma (PRP) was made by centrifuging the blood at 150–200 g for 1 minute and used for platelet studies. Platelet-poor plasma (PPP) was made by centrifugation at 2000 g for 10 minutes and used for coagulation studies. Two milliliters of blood was collected in ethylenediaminetetraacetic acid (EDTA) vial for complete blood count by autoanalyzer. Complete blood count, bleeding time (modified Ivy method), and clotting time. Coagulation profile like prothrombin time (PT), activated partial thromboplastin time (APTT), and FVIII:C assay was done manually as described by Laffan et al.[4] Platelet count, von Willebrand factor (vWF:Ag) antigen assay (ELISA, Diagnostica Stago, France), vWF:Ag, collagen binding (CB) by ELISA) were also done. The criteria for diagnosing vWD were low vWF:Ag, low FVIII activity + prolonged APTT + raised BT, abnormal "ristocetin-induced platelet aggregation" (RIPA), and any two of these tests found abnormal were taken as diagnostic of vWD.

Platelet aggregation study with ristocetin using dual-channel chronolog platelet aggregometer [ristocetin (Sigma) concentration of 1.5 mg/mL] was carried out to find different subtypes of vWD as per the criteria used in Table 1. Low-dose RIPA (0.5 mg/mL, RIPA-LD) was also done wherever indicated to rule out type IIB vWD/or platelet-type vWD.

The statistical analysis was done using SPSS 26 software. Student's *t*-test and Mann–Whitney *U* test were applied to know the significance according to suitability of data.

Results

The mean age of menarche in the patients diagnosed with vWD was significantly earlier than among controls (11.56 ± 0.71 vs 12.4 ± 0.8 years, respectively). The patients diagnosed with vWD were also much younger had significantly prolonged menses with shorter cycle length and lower hemoglobin levels (Table 2). The associated bleeding symptoms were present in 20% and family history of increased menses in 21% of the patients with HMB as compared to none among the controls. Among the associated bleeding symptoms in patients with HMB, prolonged bleeding on minor cut/trauma was the most common (20%), followed by petechiae/ecchymosis (19%), bruise (17.5%), epistaxis (15%), and bleeding from gums (12.5%). However, among the patients with vWD, 84% (21/25) had one or more associated bleeding symptoms. The most common among them was prolonged bleeding on cut/trivial trauma (84%), followed by bruise (64%), ecchymosis (60%), gingival bleeding (24%), and epistaxis (16%).

vWD and its subtypes were diagnosed in 25 out of 200 women with HMB (12.5%) out of whom the majority were below 20 years of age (12, 48%), followed by 10 (40%) in 20–44 years of age-group, and

Table 1: Diagnostic criteria for vWD subtypes

Types of vWDs	*Inheritance*	*Platelet count*	*PT*	*APTT*	*BT*	*FVIII:C*	*vWF:Ag*	*RIPA*	*RIPA-LD*
I	AD	N	N	N/↑	N/↑	↓	↓	N to ↓	Absent (—)
IIA	AD	N	N	N/↑	N/↑	N to ↓	N to ↓	↓↓	—
IIB	AD	˅	N	N/↑	↑	N to ↓	N to ↓	↑	↑
IIM	AD	N	N	N/↑	↑	N to ↓	N to ↓	↓	—
IIN	AR	N	N	↑	↑↑	↓	N to ↓	N to ↓	—
III	AR	N	N	↑	↑	↓↓	↓↓	↓↓	—

vWD, von Willebrand disease; RIPA, ristocetin-induced platelet aggregation; LD, low dose; FVIII:C, factor VIII procoagulant activity; vWF:Ag, Ag-von Willebrand factor antigen

Table 2: Clinical and laboratory characteristics of HMB patients with vWD and controls (mean ± SD)

		Mean ± SD			
Sl. No.	*Parameters*	*vWD (n = 25)*	*Control (n = 200)*	*"t" value*	*"p" value*
1	Age (years)	22.56 ± 9.96	29.70 ± 9.89	3.399	0.001
2	Age at menarche (years)	11.56 ± 0.71	12.4 ± 0.80	4.995	<0.001
3	Duration of menses (days)	8.72 ± 0.79	4.40 ± 0.80	25.427	0.001
4	Length of cycle (days)	22.44 ± 1.04	28.00 ± 1.62	16.748	0.001
5	Hb. (gm%)	6.47 ± 1.09	11.11 ± 0.78	26.775	0.001
6	BT (minutes)	10.20 ± 2.65	3.17 ± 0.52	33.199	0.001
7	CT (minutes)	4.3 ± 0.30	4.20 ± 0.29	1.724	0.086
8	PT (seconds)	13.82 ± 0.88	12.77 ± 0.91	5.474	0.001
9	APTT (seconds)	58.56 ± 21.63	31.53 ± 1.01	17.792	0.001
10	RIPA (%)*	55.16 ± 19.93	87.14 ± 3.69	20.344	0.001
11	vWF:Ag (%)	23.07 ± 14.14	109.80 ± 12.52	32.181	<0.001
12	FVIII (%)	53.156 ± 33.90	128.70 ± 15.23	$Z = 8.176^{**}$	<0.001
13	Platelet count lack/mm^3	2.8 ± 0.51	3.00 ± 0.49	1.923	0.056 NS

*Could be done in 25 patients and 50 controls. Hb, hemoglobin; **Mann–Whitney *U* test; APTT, activated partial thromboplastin time; BT, bleeding time

only 3 (12%) beyond the 44 years of age. Among the vWD patients, type III vWD was the commonest (15, 60%), followed by type IIN in five (20%), type I in three (12%), and type IIA and M in one each (4% each). None of our patients with vWD had type IIB. The PT, APTT, RIPA, and vWF:Ag antigen levels were significantly lower in the patients diagnosed with vWD as compared to controls (Table 2).

In short, the patients with low vWF:Ag (<40%), and normal to reduced RIPA were considered to have type I vWD. The patients with prolonged BT and APTT, marked reduction in FVIII:C assay, reduced vWF:Ag level, and abnormal RIPA were attributed to having type III vWD.

Discussion

The vWF:Ag is synthesized in the endothelial cells of blood vessels and in megakaryocytes. The Weibel–Palade bodies in the endothelial cells and the α-granules of the platelets act as their storehouse. It circulates in the plasma in the form of vWF:Ag FVIII:C complex. It plays a direct role in thrombin and fibrin generation by acting as a carrier molecule for the cofactor FVIII. Its two most important functions are (i) facilitation of the adhesion of platelets to subendothelium at the site of injury—primary hemostasis and (ii) stabilization of FVIII:C in circulation which thereby increases its half-life 5–10 times—secondary hemostasis.

The vWD is the most common, predominantly autosomal dominant, and an inherited bleeding disorder. It affects approximately 1% of the general population.[5] Symptomatic vWD has been reported to be still less (0.01% of general population).[6] It may result from quantitative deficiency (type I and III) as well as qualitative defect (type II) of vWF:Ag. Its level in blood may vary in the same woman at different phases of the menstrual cycle.

We, as well as others, find the prevalence of vWD to be much higher (10–20%) among the women with HMB referred to a tertiary care hospital.[3] Shankar et al. found the prevalence of vWD in women with HMB in the range of 5–24%, with an overall prevalence of 13% (95% confidence interval [CI], 11–16%) on the basis of a systematic review of 11 studies encompassing 988 women with menorrhagia.[3] This is not far from our finding of vWD in 12.5% of the women suffering from HMB. On the contrary, the prevalence of HMB in women with vWD has been reported to vary from 74 to 92%.[7]

The mean age of the patients in the present study was 22.56 ± 9.96 years, mostly teenagers (48%), and all three patients more than 44 years old (12%) had type I vWD. Kumar et al. found 17 out of 23 women (73.91%) with vWD in the reproductive age-group of 18–45 years.[8] The difference between the two studies could be due to our focus on the detection of bleeding disorder only among females with HMB. The mean age of patients in a study by Kushwaha et al. was 26.2 ± 8.6 years.[9] They reported the mean age of menarche of their patients as 11.6 ± 0.86 years comparable with the age of menarche in our patients with vWD, 11.56 ± 0.71 years. Payandeh et al. in a study of 482 women with menorrhagia (mean age: 24.4 ± 8.9 years) found 11.6% of them suffering from inherited bleeding disorders and among them 55.3% had vWD.[10] The mean duration of the menstrual cycle in our patients (8.72 ± 0.79) was almost similar to that reported by Kushwaha et al. (9.33 ± 2.36) indicating that the patients with vWD are likely to have younger age of menarche and longer duration of cycle than their normal counterparts. This together with microcytic hypochromic anemia among them makes it an important public health issue. Further, the hemostatic challenge of childbirth may add to their compromised nutrition and seek the attention of the healthcare providers at different levels.

The inherited bleeding disorders were found in 27% of our women with HMB and vWD was the commonest among them (46.29%). In another study too, 29% of the women suffering from HMB had an underlying bleeding disorder.[11] Dilley et al., however, reported inherited bleeding disorders in 10.7% of women with menorrhagia and 61.5% of them had vWD.[12] But, Kushwaha et al. found 22% of their 21 patients with bleeding disorder and 43.4% of them had vWD.[9] A study from Western India showed a prevalence of approximately 10% of vWD among all inherited bleeding disorders.[13]

All said and done, the diagnosis of vWD is not straightforward. Besides the HMB, history of bleeding symptoms in the same individual, often with a family history of bleeding symptoms or diagnosed vWD, should make the reasonable background to initiate confirmatory laboratory testing. Typical bleeding includes mucosal bleeding symptoms such as easy bruising, epistaxis, gingival bleeding, surgical bleeding, and HMB. Gastrointestinal bleeding is a particular problem for patients having type IIA vWD. Type III and type IIN vWD patients may have joint bleeds due to low FVIII and need to be differentiated from Hemophilia. As every laboratory assay has got some limitations, no single test procedure is enough to detect all the variants of vWD. That is why vWD still remains an underdiagnosed disease entity in our country.

As vWF:Ag levels have been found to increase with age, it is quite logical for us to find only three patients beyond 44 years old and that too with a milder form of type I vWD. Sharma and Floods feel that it is also possible that higher vWF:Ag levels are required for hemostasis as the patients age advances.[14]

Although the history of mucosal bleeding is an important triggering factor to investigate for vWD, one should keep the possibility of platelet function defects (PFD), FVIII carrier state, vascular malformations such as hereditary hemorrhagic telangiectasias, and some connective tissue disorders also in the list of differential diagnosis. Gupta et al. found vWD to be less common as compared to PFD (16.7 vs 35.6%) which was also the case with Sahoo et al. who had vWD in 4.4% as compared to PFD in 7.5%.[15,16] The associated bleeding symptoms found in 28 of our 200 patients (14%) with HMB were due to vWD (10/25, 40%), FVIII carrier state (11/22, 50%), and platelet function disorder (7/7, 100%).

Kumar et al.[8] found the associated bleeding symptoms in about 47% of the patients (8/17) with vWD in contrast to 40% of our vWD patients who reported one or the other associated bleeding symptom such as prolonged bleeding from minor cut/trauma (84%), easy bruising (64%), ecchymosis (60%), bleeding gums (24%), and epistaxis (16%). In a study by Kushwaha et al., 30.76% of the patients gave history of other bleeding tendencies associated with menorrhagia with epistaxis as the most common (46.9%) followed by gum bleeding (15.6%) and excessive bleed from wound (15.6%).[9] One-fifth of our patients with HMB (42, 21%) had a positive family history of bleeding disorder. However, Kumar et al. reported positive family history in 30% of the affected patients.[8] Since the diagnosis of vWD is not attempted in many of the laboratories in India and is cumbersome and costly, the treating physician should always make the presumption of this entity in patients with HMB particularly if one or the other bleeding symptom is associated or if there is a positive family history. At the same time, a negative family history does not rule out vWD in a woman with HMB because of incomplete penetrance and variable expression.[17]

Most of the studies, especially from the Western world, report type I vWD to be the most common vWD type, followed by type II and type III (Table 3).[18–24] The classical distribution of vWD types in the Western population is 60–80% type I, 7–30% type II, and 5–20% type III vWD.[11] On the contrary, the studies from India have variable representations of various vWD types among the hospital-based patients. Some including us report type III to be commoner than other types, whereas Kumar et al. found type I to be the most common (Table 4).[8,15,25–27]

By and large, one can say that the studies from the Western developed world report type I to be the commonest and the others from the developing countries including India find type III to be more common. One should keep in mind the fact that many centers in the world and especially in our country do not have the facility for multimer analysis that may result in false reporting of some type II vWD cases as type I. In one study, many patients who were once labeled as type I vWD were later diagnosed as type II vWD after reviewing with multimeric analysis.[28] Thus, the multimeric analysis is a sensitive method for correct subtyping of vWD. However, we could not carry out multimeric analysis due to financial constraints. We categorized patients with low vWF:Ag (<40%) with normal to reduced RIPA as type I vWD and those with normal to low vWF:Ag (>40%) and markedly diminished RIPA as type IIA vWD. We agree that there may be some overlapping between these two categories of patients in our study.

Due to limited availability of multimer analysis, an alternative approach suggested to distinguish between types IIA and M is to use ratios of vWF:Ag activity and vWF:Ag CB to vWF:Ag.[29] Meiring et al. found type II vWD to be the most common type (58%) out of which 23% were diagnosed with type IIA (defects in multimerization), 22% with type IIB (defective spontaneous platelet binding), 13% with type IIM (defects in ligand binding with intact multimers), and none with type IIN (defects in FVIII binding).[24] However, among 28% of our type II vWD patients, type IIN was the most common (20%), followed by type IIA and type M (each 4%) and none with type IIB. Among type II vWD, Kumar et al. reported type IIA as the most common type found in 10 patients and only one patient of type IIN.[8] They did not find any patient with type IIB or type IIM. Most of the studies from India report a high prevalence of type II and type III vWD, i.e., much more severe forms of diseases than type I vWD. However, very few go into details of various subtypes of type II vWD. It is important to realize that vWD in India may not be diagnosed with its true prevalence because of the mild bleeding symptoms or because HMB may be regarded by the patient as normal particularly if several members in the family had it. That is perhaps also the reason as to why so many authors from our country find type I vWD to be the least common subtype in their patients.

It is important to mention that ristocetin may be altogether avoided by using the vWF:Ag GPIbM assay.[30] This assay is not only more precise but also detects much lower level of 2 IU/dL of vWF:Ag. Although an accurate subtyping of vWD requires a series of laboratory investigations, one should emphasize on the practical management aspects rather than insist for getting the molecular classification of vWD subtypes. It is all the more true for our social system where the women particularly from rural background, poor financial status, and underprivileged section of the society are nutritionally compromised and suffer from anemia which need correction on priority.

Conclusion

Thus, vWD was found to be a common bleeding disorder (12.5%) in the patients referred to us with HMB, and among them, type III was the most frequent type (60%). Since menstruation and childbirth are the two important hemostatic challenges that a woman comes across in her life, it is important to either establish or rule out the diagnosis of vWD much before one has to face the real challenge

Table 3: Prevalence of vWD in Western countries

Authors	*Country*	*Patients with vWD*	*Type I (%)*	*Type II (%)*	*Type III (%)*
Rodgers et al.[18]	South Australia	General population	52	44	5
Lanke et al.[19]	South GDR	111	76	12	12
Nilsson[20]	Sweden	106 families	70	10	20
Howard and Firkin[21]	Sweden	116	71	23	6
Awidi[22]	Jordan	65	59	29.5	11.5
Federici et al.[23]	Italy	1,234	63	32	5
Meiring et al.[24]	South Africa	250	38	58	4

Table 4: Prevalence of vWD reported by Indian authors

Study	*Inherited bleeding disorder/HMB (No.)*	*vWD No. (%)*	*Type I No. (%)*	*Type II No. (%)*	*Type III No. (%)*
Trasi et al.[25]	822	81 (9.8)	15 (18.5)	16 (19.7)	50 (61.7)
Gupta et al.[26]	224	64 (28.6)	14 (21.9)	28 (43.7)	21 (32.8)
Gupta et al.[15]	872	94 (16.8)	20 (21.3)	42 (44.7)	32 (34)
Ahmad et al.[27]	1,576	135 (8.6)	29 (21.3)	73 (53.6)	33 (24.3)
Kumar et al.[8]	230	40 (17.3)	17 (42.5)	11 (27.5)	12 (30.0)
Present study 2021	200	25 (12.5)	3 (12)	7 (28)	15 (60)

and thus prepare for it much in advance. It is imperative to search for inherited bleeding disorder in the presence of associated bleeding symptoms or even a positive family history. A timely and accurate diagnosis may significantly simplify the level of care and management in these patients and also improve their quality of life and reproductive potential.

Clinical Significance

It is imperative to look for a bleeding disorder in patients with HMB particularly if they suffer from it since their menarche and in the presence of associated bleeding symptoms, and positive family history of HMB after being ruled out to have any structural or hormonal etiology. This would help the treating gynecologist to plan a definite line of management and save such patients from misery of repeated heavy blood loss, nutritional deficiency, psychosocial factors, and unnecessary hysterectomies.

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